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(54) Title: INDOLE AND INDAZOLE UREA-PEPTOIDS AS THROMBIN RECEPTOR ANTAGONISTS

(57) Abstract: The invention is directed to novel indole and indazole urea-peptoid compounds which are useful as thrombin receptor antagonists for the treatment of diseases associated with thrombosis, restenosis, hypertension, heart failure, arrhythmia, inflammation, angina, stroke, atherosclerosis, ischemic conditions, Angiogenesis related disorders, cancer, and neurodegenerative disorders. Pharmaceutical compositions comprising the substituted indole and indazole urea-peptoid compounds of the present invention and methods of treating conditions mediated by the thrombin receptor are also disclosed.

INDOLE AND INDAZOLE UREA-PEPTOIDS AS THROMBIN RECEPTOR ANTAGONISTS

5 FIELD OF THE INVENTION

This invention relates to certain novel thrombin receptor antagonists, their synthesis and their use for the treatment of diseases associated with thrombosis, restenosis, hypertension, heart failure, arrhythmia, inflammation, angina, 10 stroke, atherosclerosis, ischemic conditions, Angiogenesis related disorders, cancer, and neurodegenerative disorders.

BACKGROUND OF THE INVENTION

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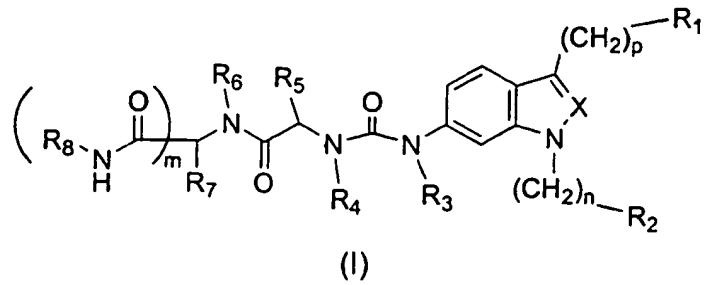
Thrombin is an important serine protease in hemostasis and thrombosis. One of the key actions of thrombin is cellular modulation via receptor activation. A functional human thrombin receptor (PAR-1), cloned by Coughlin in 1991 (T.-K. Vu, *Cell* 1991, 64, 1057), was found to be a member of the 20 G-protein coupled receptor (GPCR) superfamily. The receptor activation putatively occurs by N-terminal recognition and proteolytic cleavage at the Arg-41/Ser-42 peptide bond to reveal a truncated N-terminus. This new receptor sequence, which has an SFLLRN (Ser-Phe-Leu-Leu-Arg-Asn) N-terminus acting as a tethered ligand to recognize a site on the receptor, can 25 trigger activation and signal transduction leading to platelet aggregation. Since 1991, three other protease-activated receptors with extensive homology to the thrombin receptor, "PAR-2" (S. Nystedt, *Proc. Natl. Acad. Sci USA* 1994, 91, 9208), "PAR-3" (H. Ishihara, *Nature* 1997, 386, 502), and "PAR-4" (W.-F. Xu, *Proc. Natl. Acad. Sci USA* 1998, 95, 6642), have been cloned. Thrombin 30 receptor (PAR-1) specific antibody-induced blockade of the platelet thrombin receptor has shown efficacy against arterial thrombosis *in vivo* (J. J. Cook *Circulation* 1995, 91, 2961). Hence, antagonists of the thrombin receptor (PAR-1) are useful to block these protease-activated receptors and, as such, may be used to treat platelet mediated thrombotic disorders such as 35 myocardial infarction, stroke, restenosis, angina, atherosclerosis, and ischemic conditions.

The thrombin receptor (PAR-1) has also been identified on other cell types: endothelial, fibroblast, renal, osteosarcoma, smooth muscle, myocytes, tumor, and neuronal/glia. Thrombin activation of endothelial cells upregulates 5 P-selectin to induce polymorphonuclear leukocyte adhesion - an inflammatory response of the vessel wall (Y. Sugama, *J. Cell Biol.* 1992, 119, 935). In fibroblasts, thrombin receptor (PAR-1) activation induces proliferation and transmission of mitogenic signals (D. T. Hung, *J. Cell Biol.* 1992, 116, 827). Thrombin has been implicated in osteoblast proliferation through its activation 10 of osteoblast cells (D. N. Tatakis, *Biochem. Biophys. Res. Commun.* 1991, 174, 181). Thrombin has been implicated in the regulation and retraction of neurons (K. Jalink, *J. Cell. Biol.* 1992, 118, 411). Therefore, in this context, the antagonist compounds of this invention may also be useful against 15 inflammation, osteoporosis, Angiogenesis related disorders, cancer, neurodegenerative disorders, hypertension, heart failure, arrhythmia, glomerulonephritis.

The compounds of the present invention are a structurally novel class of indole and indazole urea-peptoids represented by the general formula (I) below.

SUMMARY OF THE INVENTION

The present invention is directed to structurally novel compounds represented by the following general formula (I):



wherein:

30

R₁ is selected from amino, C₁-C₈ alkylamino, C₁-C₈ dialkylamino, arylamino, arC₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, heteroalkylC₁-C₈ alkylamino, heteroalkylC₁-C₈ alkyl-N-methylamino, C₁.C₈ dialkylamino C₁.C₈ alkylamino, -N(C₁-C₈ alkyl)-C₁-C₈ alkyl-N(C₁-C₈ alkyl)₂, -N(C₁.C₈ alkyl)(C₁.C₈ alkenyl), -N(C₁-C₈ alkyl)(C₃-C₈ cycloalkyl), heteroalkyl or substituted heteroalkyl, wherein the substituent on the heteroalkyl is selected from oxo, amino, C₁-C₈ alkoxy, C₁-C₈ alkyl, C₁-C₈ alkylamino or C₁.C₈ dialkylamino;

R₂ is selected from unsubstituted or substituted aryl, arC₁-C₈ alkyl, C₃.C₈cycloalkyl or heteroaryl, wherein the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁.C₈alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl;

15

R₃ is selected from H or C₁-C₈ alkyl;

R₄ and R₅ are each selected from H, C₁-C₈ alkyl, amino C₁-C₈ alkyl, amidino C₁-C₈ alkyl, guanidino C₁-C₈ alkyl, aryl, aryl C₁-C₈ alkyl, substituted 20 aryl, substituted arylC₁.C₈ alkyl, heteroaryl, heteroaryl C₁-C₈ alkyl, substituted heteroaryl, substituted heteroaryl C₁-C₈ alkyl, cyclo C₃-C₈ alkyl or substituted cycloC₃.C₆alkyl, wherein the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, 25 C₁-C₈ alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl;

R₆ and R₇ are each selected from H, C₁-C₈ alkyl, amino- C₁-C₈ alkyl, amino- C₃-C₈ cycloalkyl, amidino C₁-C₈ alkyl, guanidino C₁-C₈ alkyl, aryl, substituted aryl, aryl C₁-C₈ alkyl, substituted aryl C₁-C₈ alkyl, heteroaryl C₁-C₈ alkyl or substituted heteroaryl C₁-C₈ alkyl, wherein the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₈

alkyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl;

Either R₅ or R₇ must be H when m is 1; in addition, when R₅ is H, then R₄ 5 cannot be H; and, when R₇ is H, then R₆ cannot be H;

R₈ is selected from H, C₁-C₈ alkyl, amino C₁-C₈ alkyl, allyl, C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl, aryl, substituted aryl, ar C₁-C₈ alkyl, substituted ar C₁-C₈ alkyl, heteroaryl, substituted heteroaryl, heteroaryl C₁-C₈ 10 alkyl or substituted heteroaryl C₁-C₈ alkyl, wherein the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl;

15

X is CH or N;

n is an integer selected from 0, 1, 2 or 3;

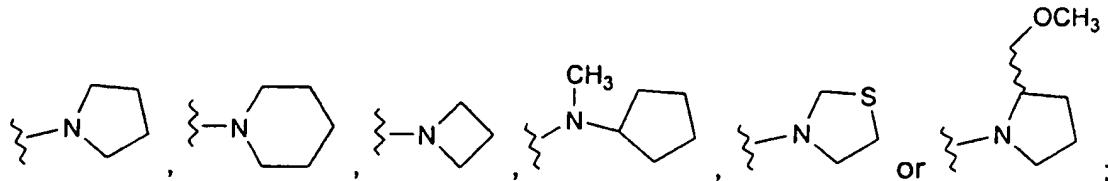
m is an integer selected from 0 or 1;

20 p is an integer selected from 1 or 2; and,

pharmaceutically acceptable salts thereof.

In one embodiment of the invention is the compound of formula (I) 25 wherein

R₁ is selected from dimethylamino, diethylamino, di-(n-propyl)amino,



preferably, R₁ is

R_2 is selected from unsubstituted or substituted aryl, arC₁-C₆ alkyl, C₃-C₆ cycloalkyl or heteroaryl, where the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one to three substituents

5 selected from halogen, cyano, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl; preferably, R_2 is unsubstituted or substituted phenyl wherein the substituent is one or two substituents selected from fluorine, chlorine, iodine, methyl, cyano or trifluoromethyl;

10

R_3 is selected from H or C₁-C₄ alkyl; preferably, R_3 is H;

R_4 and R_5 are each independently selected from H, C₁-C₄ alkyl, aminoC₁-C₆ alkyl, amidinoC₁-C₆ alkyl, guanidinoC₁-C₆ alkyl, aryl, arC₁-C₈ alkyl,

15 substituted aryl, or substituted arC₁-C₈ alkyl, wherein the substituents on the aryl or aralkyl are independently selected from one or two of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl;

20

R_6 and R_7 are each independently selected from H, C₁-C₄ alkyl, aminoC₁-C₆ alkyl, amidinoC₁-C₆ alkyl, guanidinoC₁-C₆ alkyl, aryl, substituted aryl, arC₁-C₆ alkyl, substituted arC₁-C₆ alkyl, C₃-C₆ cycloalkylC₁-C₆ alkyl, heteroarylC₁-C₆ alkyl or substituted heteroarylC₁-C₆ alkyl, wherein the substituents on the aryl, aralkyl, or heteroaryl group are independently selected from one or two of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl;

30 preferably, R_4 , R_5 , R_6 , and R_7 are each independently selected from H, aminoC₁-C₅ alkyl, amidinoC₁-C₅ alkyl, guanidinoC₁-C₅ alkyl, C₃-C₆ cycloalkylC₁-C₆ alkyl, heteroarylC₁-C₆ alkyl, benzyl or substituted benzyl wherein the

substituents on the benzyl are independently selected from one or two of chlorine, fluorine, methyl or trifluoromethyl;

5 R_8 is selected from H, C₁-C₆ alkyl, aminoC₁-C₆ alkyl, aryl, substituted aryl, arC₁-C₆ alkyl, or substituted arC₁-C₆ alkyl, wherein the substituents on the aryl or aralkyl group are independently selected from one or more of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy or C₁-C₄ alkylsulfonyl; preferably, R_8 is benzyl;

10

 n and p are both 1;

provided that when m is one, then one of R_5 or R_7 must be hydrogen;

15 and provided further that when R_5 is hydrogen, then R_4 cannot be hydrogen; and, when R_7 is hydrogen, then R_6 cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

20 In a class of the invention is the compound wherein

R_2 is 2,6-dichlorophenyl;

25 and all other variables are as defined above;

provided that when m is one, then one of R_5 or R_7 must be hydrogen;

30 and provided further that when R_5 is hydrogen, then R_4 cannot be hydrogen; and, when R_7 is hydrogen, then R_6 cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

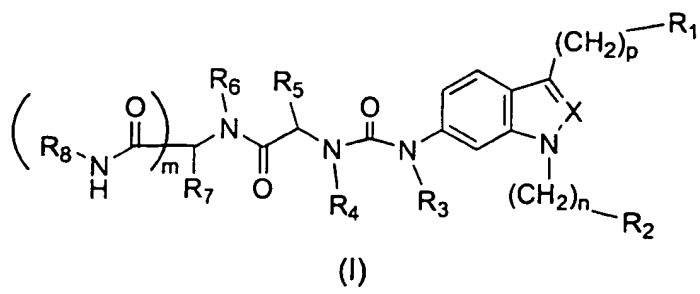
Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Illustrating the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier.

An example of the invention is a method of treating a disorder (preferably, a platelet-mediated thrombotic disorder) selected from arterial and/or venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and/or angioplasty, inflammation, unstable angina, stroke, restenosis, atherosclerosis, ischemic conditions, hypertension, heart failure, arrhythmia, glomerulonephritis, osteoporosis, Angiogenesis related disorders, cancer, neurodegenerative disorders or a variety of vaso-occlusive disorders in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. In a preferred embodiment, the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.

Also included in the invention is the use of any of the compounds described above for the preparation of a medicament for a disorder (preferably, a platelet-mediated thrombotic disorder) selected from arterial and/or venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and/or angioplasty, inflammation, unstable angina, stroke, restenosis, atherosclerosis, ischemic conditions, hypertension, heart failure, arrhythmia, glomerulonephritis, osteoporosis, Angiogenesis related disorders, cancer, neurodegenerative disorders or a variety of vaso-occlusive disorders in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

More particularly, the present invention is directed to compounds of the following formula (I):



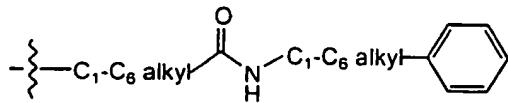
5

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, X, m, n, and p are as previously defined.

The compounds of the present invention are thrombin receptor antagonists
10 and as such are useful in treating thrombosis, restenosis, hypertension, heart
failure, arrhythmia, myocardial infarction, glomerulonephritis, reocclusion
following thrombolytic therapy, reocclusion following angioplasty, inflammation,
angina, stroke, atherosclerosis, ischemic conditions, a vaso-occlusive disorder,
neurodegenerative disorders, Angiogenesis related disorders and cancer.
15 These compounds are also useful as antithrombotics in conjunction with
fibrinolytic therapy (e.g., t-PA or streptokinase).

When a particular group is "substituted" (e.g., Phe, aryl, heteroalkyl,
20 heteroaryl), that group may have one or more substituents, preferably from one
to five substituents, more preferably from one to three substituents, most
preferably from one to two substituents, independently selected from the list of
substituents.

Under standard nomenclature used throughout this disclosure, the
25 terminal portion of the designated side chain is described first, followed by the
adjacent functionality toward the point of attachment. Thus, for example, a
"phenylC₁-C₆ alkylamidoC₁-C₆ alkyl" substituent refers to a group of the formula



The compounds of the present invention may also be present in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, 10 salicylic, saccharinic or trifluoroacetic.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., 20 hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, 25 observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes 30 alleviation of the symptoms of the disease or disorder being treated.

As used herein, unless otherwise noted alkyl and alkoxy whether used alone or as part of a substituent group, include straight and branched chains

having 1 to 8 carbon atoms, or any number within this range. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, *t*-butyl, *n*-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, *n*-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Cycloalkyl groups contain 3 to 8 ring carbons and preferably 5 to 7 carbons. Similarly, alkenyl and alkynyl groups include straight and branched chain alkenes and alkynes having 1 to 8 carbon atoms or any number within this range.

10

The term "aryl" as used herein refers to an unsubstituted or substituted aromatic group such as phenyl and naphthyl.

The term "heteroalkyl" as used herein represents an unsubstituted or substituted stable three to seven membered monocyclic saturated ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S, and wherein the nitrogen or sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroalkyl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroalkyl groups include, but are not limited to azetidinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxoazepinyl, azepinyl, tetrahydrofuranyl, dioxolanyl, tetrahydroimidazolyl, tetrahydrothiazolyl, tetrahydrooxazolyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and oxadiazolyl.

Preferred heteroalkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azetidinyl and tetrahydrothiazolyl.

30 The term "heteroaryl" as used herein represents an unsubstituted or substituted stable five or six membered monocyclic aromatic ring system or an unsubstituted or substituted nine or ten membered benzo-fused heteroaromatic ring system or bicyclic heteroaromatic ring system which consists of carbon

atoms and from one to four heteroatoms selected from N, O or S, and wherein the nitrogen or sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroaryl group may be attached at any heteroatom or carbon atom that results in the creation of a stable structure. Examples of heteroaryl groups include, but are not limited to pyridyl, pyridazinyl, thienyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, benzoxazolyl, benzopyrazolyl, indolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl adeninyl or quinolinyl.

10 Preferred heteroaryl groups include pyridyl, pyrrolyl, pyrazinyl, thiadiazolyl, pyrazolyl, thienyl, triazolyl and quinolinyl.

The term "aralkyl" means an alkyl group substituted with one, two or three aryl groups (e.g., benzyl, phenylethyl, diphenylmethyl, triphenylmethyl).

15 Similarly, the term "aralkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy). The term aminoalkyl refers to an alkyl group substituted with an amino group (i.e., -alkyl-NH₂). The term "alkylamino" refers to an amino group substituted with an alkyl group (i.e., -NH-alkyl). The term "dialkylamino" refers to an amino group which is disubstituted with alkyl groups 20 wherein the alkyl groups can be the same or different (i.e., -N-[alkyl]₂).

The term "acyl" as used herein means an organic radical having 1 to 6 carbon atoms (branched or straight chain) derived from an organic acid by removal of the hydroxyl group.

25

The term "oxo" refers to the group =O.

The term "carbonyl" refers to the group C(O).

30

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, dialkylamino) it shall be interpreted as

including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁-C₆) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

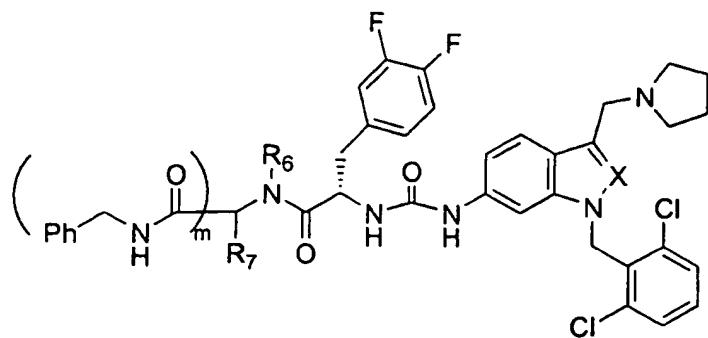
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It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. Accordingly, pharmaceutical compositions containing the compounds of the present invention as the active ingredient as well as methods of preparing the instant compounds are also part of the present invention.

Particularly preferred representative compounds of the present invention and their biological data are shown in Table 1 and Table 2, following. Table 1 and Table 2 each contain IC₅₀ values (M) against platelet aggregation stimulated by thrombin and IC₅₀ values (M) of the compounds in a thrombin receptor binding assay. The assays used to determine the biological data for the instant compounds are further described herein.

Table 1
Thrombin Receptor Antagonists



5

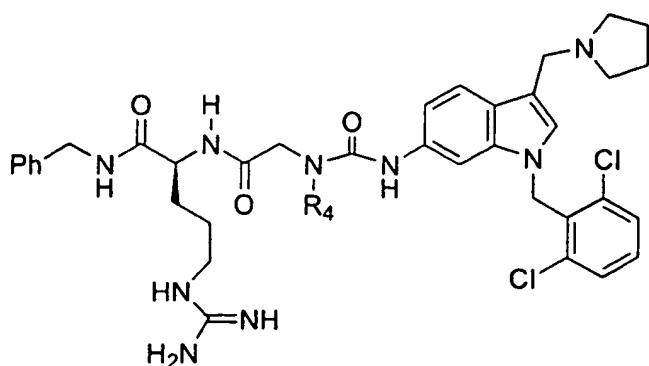
Cmp d	R ₆	X	R ₇	m	GFP Aggr.*	Recptr Bdg.**
					IC50, M	IC50, M
1	(CH ₂) ₂ NH ₂	N	H	1	1.3	0.5
2	(CH ₂) ₂ NH ₂	CH	H	1	1.7	0.3
3	(CH ₂) ₄ NH ₂	N	H	1	0.26	0.3
4	(CH ₂) ₄ NH ₂	CH	H	1	0.26	0.22
5	PhCH ₂	CH	H	1	22	0.38
6	2-ThienylCH ₂	CH	(CH ₂) ₂ NH ₂	0	0.6	10.3
7	c-C ₆ H ₁₁ CH ₂	CH	(CH ₂) ₂ NH ₂	0	1.0	8.8
8	4-PyridylCH ₂	CH	(CH ₂) ₂ NH ₂	0	0.40	29
9	H	N	(CH ₂) ₂ NH ₂	0	0.26	0.10
10	4-PyridylCH ₂	CH	(CH ₂) ₃ NH ₂	0	0.51	0.10
11	H	CH	(CH ₂) ₃ NH ₂	0	1.7	0.10

		H_2			
12	H	CH	CH_2NH_2	0	0.99
					0.07

* GFP Aggr. Thrombin-Induced Gel-Filtered Platelet Aggregation Assay

** Recptr Bdg Thrombin Receptor Binding Assay

Table 2
Thrombin Receptor Antagonists



5

Cmp d	R ₄	GFP Aggr.*		Recptr Bdg.** IC50, M
		IC50, M	IC50, M	
13	(CH ₂) ₅ NH ₂	1.0		>100
14	4-ClPhCH ₂		6.3	6.9
15	4-FPhCH ₂		2.1	8.1

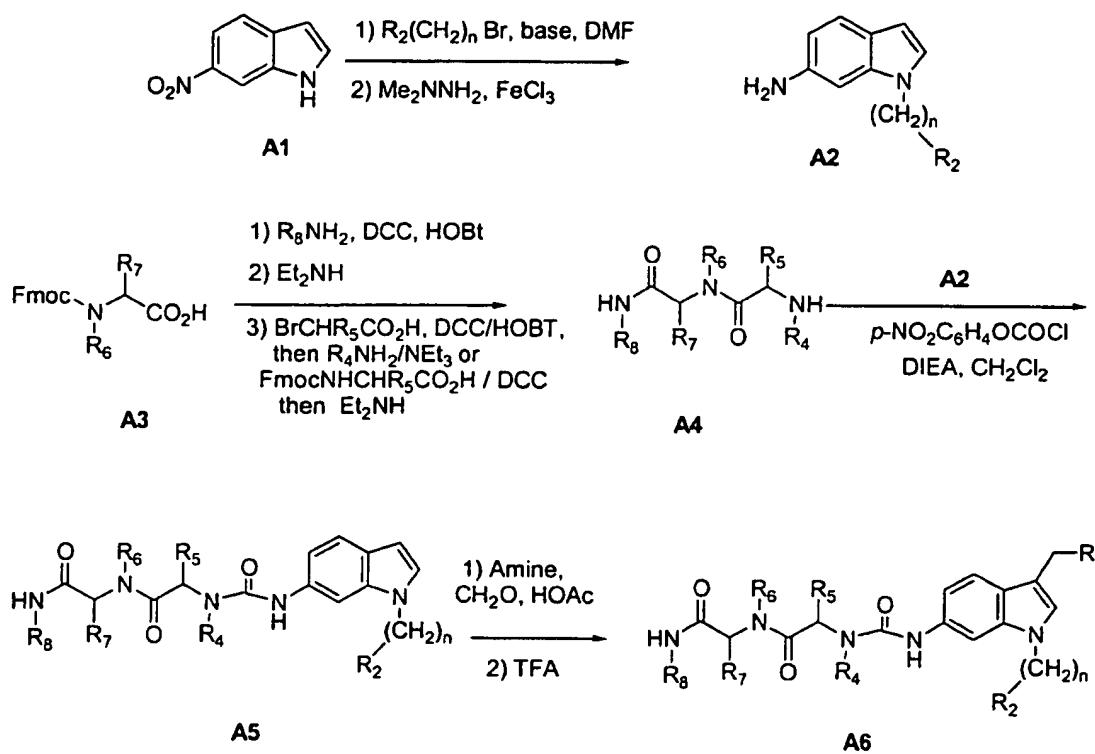
The antagonists of the present invention may be prepared via either solution-phase or solid-phase methods. In general, the compounds may be synthesized in solution following Generic Scheme A or Generic Scheme B.

10

As shown in Generic Scheme A, the 6-nitroindole **A1** may be alkylated with the appropriate halide and a base such as potassium or cesium carbonate in a dipolar aprotic solvent such as DMF or THF. Upon work-up, the crude intermediate may be reduced with a reducing agent such as iron and acetic acid or dimethyl hydrazine to give the amine **A2**. The Fmoc protected amino-acid **A3**, which may be commercially available or prepared by alkylation of R_6NH_2 with a 2-bromo acetic acid followed by Fmoc protection, is coupled to an R_8 substituted amine using classical coupling agents such as DCC or DIC with HOBT in a dipolar aprotic solvent such as ACN or DMF. The Fmoc group is removed with a secondary amine such as diethylamine in a dipolar aprotic

solvent such as ACN or DMF. The resultant amine may then be coupled with bromoacetic acid in DCC and the intermediate bromide alkylated with a R_4 substituted amine in the presence of triethylamine to afford the amine **A4**. Alternatively, the amine may be coupled with another Fmoc protected amino-acid followed by Fmoc deprotection to afford the amine **A4**. The amine **A2** is reacted with a phosgene equivalent such as 4-nitrophenyl chloroformate, phosgene or "COCl₂," phenyl chloroformate, triphosgene or "(CCl₃O)₂CO," carbonyldiimidazole, diethyl carbonate or diphenyl carbonate and DIEA, then combined with **A4** to give the urea **A5**. The urea **A5** is then added to a preformed Mannich intermediate from reaction of an amine with formaldehyde in acetic acid to afford (after TFA deprotection of side-chains if necessary) the target **A6**.

GENERIC SCHEME A

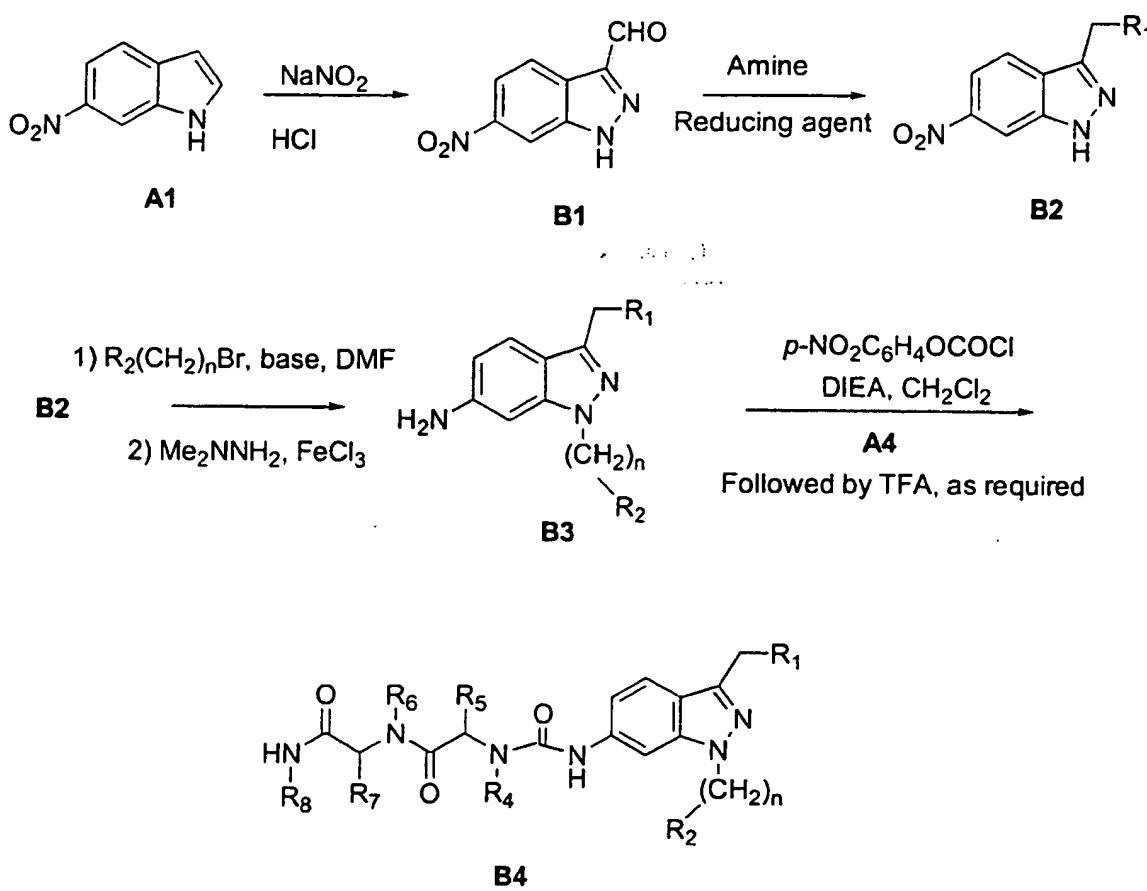


15

As shown in Generic Scheme B, the indole **A1** is converted to indazole **B1** with sodium nitrite and HCl and then reductively aminated with an amine

and a reducing agent such as sodium triacetoxyborohydride to give **B2**. **B2** was then alkylated with an appropriate alkyl halide and a base such as potassium hydroxide in a dipolar aprotic solvent such as DMF, followed by reduction of the nitro group using classical reducing agents such as tin chloride and HCl to give the amine **B3**. The amine **B3** was reacted with a phosgene equivalent and DIEA then combined with amine **A4**, as prepared above, to give the desired urea; again, deprotection of side-chain protecting groups with an acid such as TFA may be required to afford the indazole targets **B4**.

GENERIC SCHEME B



10

The side-chain amine in antagonists such as Compound 1 and Compound 6 may be converted to other functional groups such as acetamidine and guanidine by using standard procedures. For example, the acetamidine and guanidine groups can be introduced by treating the side-chain amine with

S-2-naphthylmethyl thioacetimidate hydrobromide and 2-methyl-2-thiopseudourea, respectively.

Extending the carbon chain from p being 1 to n being 2 at the 3-position of 5 the indole [see general formula (I), X = CH] may be achieved by treating the dimethylamino Mannich base (when p is 1, R₁ is NMe₂) with KCN followed by reducing the cyano group to an amine.

Extending the carbon chain from p being 1 to n being 2 at the 3-position of 10 the indazole [see general formula (I), X = N] may be introduced in the intermediate B1 (Generic Scheme B) via aldehyde-nitromethane condensation followed by reduction of the resulting -unsaturated nitro compounds to saturated amine.

15 The utility of the compounds to treat PAR-1 mediated disorders (e.g., thrombotic disorders) can be determined according to the procedures described herein. The present invention therefore provides a method of treating PAR-1 mediated disorders (e.g., thrombotic disorders) in a subject in need thereof which comprises administering any of the compounds as defined 20 herein in a quantity effective to treat PAR-1 mediated disorders. The compound may be administered to a patient by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral.

25 The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

To prepare the pharmaceutical compositions of this invention, one or 30 more compounds of formula (I) or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for

administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, for example, suspensions, elixirs and solutions, suitable carriers and additives include

5 water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration,

10 tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for

15 preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as

20 described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.03 mg/kg to about 100 mg/kg (preferred from about 0.1 mg/kg to about 30 mg/kg) of a compound of the present invention and may be given at a dosage from about 0.1 mg/kg/day to about

25 300 mg/kg/day (preferred from about 1 mg/kg/day to about 50 mg/kg/day). The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

30

Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or

suppositories for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate 5 salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums and other pharmaceutical diluents, e.g. water, to 10 form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage 15 forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.1 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of 20 prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material 25 can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention 30 may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable

dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

5 Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The 10 compounds may, for example, be resolved into their components enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by 15 formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

20 During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic 25 Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

30 The method of treating PAR-1 mediated disorders (e.g., thrombotic disorders) described in the present invention may also be carried out using a pharmaceutical composition comprising any of the compounds as defined herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 0.01 mg to about 100 mg, preferably from about 5 mg to about 50 mg of the compound and may be constituted into any form

suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, 5 tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

10 Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well 15 known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the 20 active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or 25 beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

30

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl cellulose and the like. For parenteral administration, sterile suspensions and

solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

5 The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

10 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, 15 polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block polymers of hydrogels.

20

25 Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of PAR-1 mediated disorders (e.g., thrombotic disorders) is required.

30 The daily dosage of the products may be varied over a wide range from about 0.01 mg to about 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing about 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about

100 mg/kg of body weight per day. Preferably, the range is from about 0.03 mg/kg to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of about 1 time to about 4 times per day.

5 Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of
10 administration, will result in the need to adjust dosages.

Biology

15 The compounds of the present invention are thrombin receptor (PAR-1) antagonists. The compounds interrupt platelet activation induced by thrombin's proteolytic cleavage of its platelet surface receptor, and thereby inhibit platelet aggregation. Such compounds are, therefore, useful in treating platelet-mediated thrombotic disorders (e.g., arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and
20 angioplasty, and a variety of vaso-occlusive disorders) and other PAR-1 mediated disorders.

In Vitro Thrombin Receptor Binding Assay

25 CHRF membranes (Jones, *Biochim. Biophys. Acta* 1992, 1136, 272) are thawed from -70°C, centrifuged at maximum speed for 5 min, washed twice with binding buffer (50 mM HEPES containing 5 mM MgCl₂ and 0.1% BSA), and re-suspended in binding buffer (25 g/100 mL). 100 L of membranes are added to the 24-Wallac plates and delivered to the Tomtech apparatus. In
30 a typical experiment, 6 L of samples (from a 125 g/mL intermediary plate, 20% DMSO) and 44 L buffer are delivered to the plates (final conc. of compounds is 3.7 g/mL, 0.6% DMSO). Similarly, 6 L 20% DMSO and 44 L buffer are delivered to both column 1 (NSB) and column 12 (TB). 10 L Ser-pFPhe-Har-Leu-Har-Lys-Tyr-NH₂ (721-40; 500 M in deionized water) is
35 added to column 1. 50 L tritiated 721-40 (specific activity 46 Ci/mmol) is added to all the wells. The plates are mixed well for 20 seconds, incubated for

30 min, and then harvested with 10 mM HEPES/138 mM NaCl using the Skatron harvester. The filters (GF/C Brandel FPXLR 296) are presoaked 3 h in 0.5% polyethylenimine in HEPES/0.1M N-acetylglucosamine) are set in saran wrap and dried for 3 min in the microwave, and placed in sample bags (Wallac 5 1450-432). 4.5 mL scintillation fluid (Wallac, Betaplate Scint 1205-440) is added. The bags are sealed, placed in filter cassettes (Wallac 1450-104), and analyzed on the microbeta counter.

10 ***In Vitro Inhibition Of Thrombin-Induced Gel-Filtered Platelet Aggregation Assay***

15 The percentage of platelet aggregation is calculated as an increase in light transmission of compound-treated platelet concentrate vs. control-treated platelet concentrate. Human blood is obtained from drug free, normal donors in tubes containing 0.13M sodium citrate. Platelet rich plasma (PRP) is collected by centrifugation of whole blood at 200 x g for 10 min at 25°C. The PRP (5 mL) is gel filtered through Sepharose 2B (bed volume 50 mL), and the platelet count is adjusted to 2×10^7 platelets per sample. The following constituents are added to a siliconized cuvette: concentrated platelet filtrate 20 and Tyrode's buffer (0.14M NaCl, 0.0027M KCl, 0.012M NaHCO₃, 0.76 mM Na₂HPO₄, 0.0055M glucose, 2 mg/mL BSA and 5.0 mM HEPES @ pH 7.4) in an amount equal to 350 L, 50 L of 20 mM calcium and 50 L of the test compound. Aggregation is monitored in a BIODATA aggregometer for the 3 min following the addition of agonist (thrombin 50 L of 1 unit/mL).

25

30 The biological activity for representative compounds of the present invention are as previously shown in Table 1 and Table 2.

Examples

35 **General Procedures:** Resins and protected amino acids were purchased from Novabiochem, Bachem Bioscience, Advanced ChemTech or Synthe Tech. All other chemicals were obtained from commercial suppliers and used without further purification. ¹H and ¹³C NMR spectra were recorded on a Bruker AC 300B (300 MHz proton) or a Bruker AM-400 (400 MHz proton) spectrometer with Me₄Si as an internal standard (s = singlet, d = doublet, t =

triplet, br = broad). APCI-MS and ES-MS were recorded on a VG Platform II mass spectrometer; methane was used for chemical ionization, unless noted otherwise. Accurate mass measurements were obtained by using a VG ZAB 2-SE spectrometer in the FAB mode. TLC was performed with Whatman 250-5 m silica gel plates. Preparative TLC was performed with Analtech 1000- m silica gel GF plates. Flash column chromatography was conducted with flash column silica gel (40-63 m) and column chromatography was conducted with standard silica gel. HPLC separations were carried out on three Waters PrepPak® Cartridges (25 x 100 mm, Bondapak® C18, 15-20 m, 125 Å) connected in series; detection was at 254 nm on a Waters 486 UV detector. Analytical HPLC was carried out on a Supelcosil ABZ+PLUS column (5 cm x 2.1 mm), with detection at 254 nm on a Hewlett Packard 1100 UV detector. Microanalysis was performed by Robertson Microlit Laboratories, Inc.

15 In the examples and throughout this application, the following abbreviations have the meanings recited hereinafter:

Ac	Acetyl
ACN	Acetonitrile
20 Bn	Benzyl
Boc	t-Butoxycarbonyl
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEA	Diethylamine
25 DIC	Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N, N-Dimethylformamide
Et	Ethyl
30 Fmoc	9-Fluorenylmethoxycarbonyl
h	Hour
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HOAc	Acetic acid
HOBT	Hydroxybenzotriazole
<i>i</i> -Pr or iPr	Isopropyl
Me	Methyl
5 min	Minute
Pmc	2,2,5,7,8-Pentamethylchroman-6-sulfonyl
Py	Pyridine
rt	room temperature
THF	Tetrahydrofuran
10 TFA	Trifluoroacetic acid
Tr	Triphenylmethyl

Example 1

Synthesis of Compound 15 (See Scheme AA)

15

N-4-Fluorophenylmethyl-N-[(1-(2,6-dichlorophenyl)methyl-3-(1-pyrrolidinylmethyl)-1*H*-indol-6-yl]aminocarbonyl} -glycinal-L-arginin-N-benzyl-amide (Compound 15)

20 As shown in Scheme AA, following, 6-Nitroindole **AA1** (8.0 g, 49.2 mm) was dissolved in dry DMF (60 mL) under argon, cesium carbonate (16.0 g, 49.2 mm) was added and the mixture was stirred at about 45°C for about 30 min. After cooling to about rt, the mixture was stirred while 2,6 dichlorobenzyl bromide (13.0 g, 54 mm) in DMF (40 mL) was added over about 1 h; the
 25 reaction was then stirred at about rt for about 16 h. The solution was then added portionwise to water (1.6 L) with vigorous stirring, which precipitated a solid, and stirring was continued for about 3 h. The resulting yellow solid was filtered and washed with hexane (3X) and air-dried. The solid was combined in MeOH (150 mL) with charcoal (1.1 g, 92 mm), ferric chloride hexahydrate (0.54 g, 2.0 mm) and 1,1 dimethylhydrazine (27.2 g, 440 mm) and the mixture was refluxed for about 16 h. After cooling to about rt, the reaction was filtered through dicalite and the filtrate was evaporated *in vacuo* to a yellow solid. The solid was partitioned between 1N HCl (750 mL) and diethyl ether (750 mL).

The solid was then combined with the aqueous acid solution, the pH was made greater than about pH 13 with 3N NaOH and extracted with DCM (2X, 400 mL). The DCM solution was washed with saturated NaHCO₃ (2X), brine, dried (K₂CO₃) and evaporated *in vacuo* to a solid, which was triturated with hexane (3X) to afford a light tan solid **AA2**.

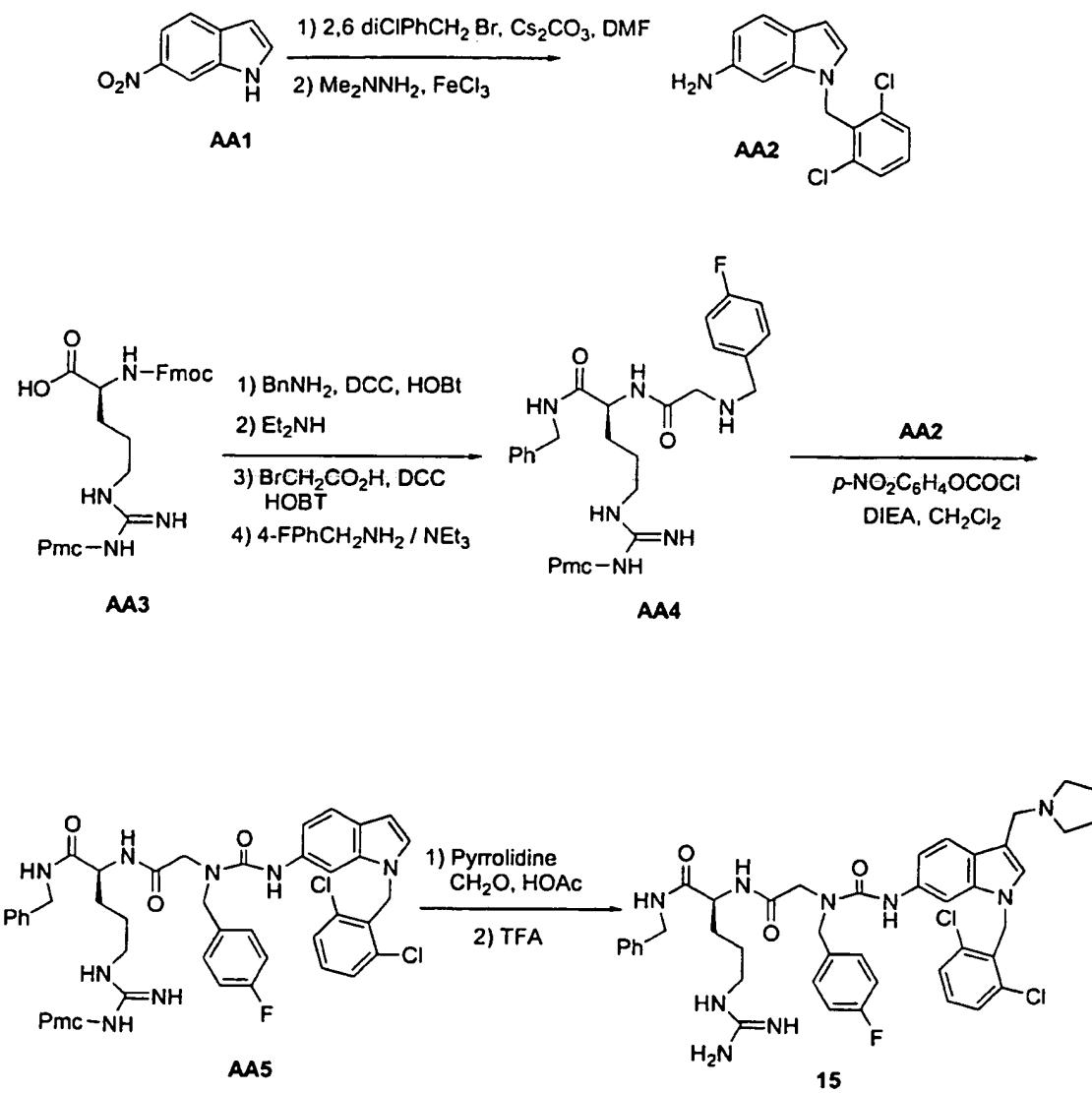
Fmoc-arginine(PMC)-OH **AA3** (3.83 g, 5.0 mm) and HOBT (0.76 g, 5.0 mm) were combined in acetonitrile (100 mL), benzylamine (0.54 g, 5.0 mm) was added in dropwise at about rt, followed by DCC (2.06 g, 10.0 mm) and stirred for about 16 h. The solid was filtered and the filtrate was evaporated *in vacuo* to an oil, which was dissolved in ethyl acetate (100 mL) and washed with saturated NaHCO₃ (2X), brine (2X), dried (Na₂SO₄) and was evaporated *in vacuo* to a solid, which was triturated with hexane (2X) to give a solid (impure with dicyclohexylurea). A portion of the solid (0.52 g, 0.70 mm) was dissolved in ACN (30 mL), diethyl amine (1.5 mL) was added and the reaction was stirred at about rt for about 1 h. The solution was evaporated *in vacuo* to a solid, which was triturated with hexane (3X) and evaporated *in vacuo* to a solid. The resulting solid was combined in ACN (20 mL) with bromoacetic acid (0.10 g, 0.70 mm) and HOBT (0.11 g, 0.7 mm). DCC (0.29 g, 1.4 mm) was added to the solution and the reaction was stirred at about rt for about 2 h. The solid was filtered and discarded and the filtrate was evaporated *in vacuo* to an oil. The oil was dissolved in ethyl acetate (25 mL) and washed with saturated NaHCO₃ (3X), brine (2X), dried (Na₂SO₄) and evaporated *in vacuo* to an oil. The resulting oil was dissolved in DCM (10 mL), 4-fluorobenzylamine (88 mg, 0.70 mm) and triethylamine (101 mg, 1.0 mm) were added and the reaction stirred at about rt for about 24 h. The solution was evaporated *in vacuo* to an oil, which was purified by column chromatography to afford amine **AA4**.

Amino-indole **AA2** (142 mg, 0.49 mm) and DIEA (63 mg, 0.49 mm) in DCM (3 mL) were added to 4-nitrophenylchloroformate (99 mg, 0.49 mm) in dry DCM (120 mL) at about -20°C and stirred at about -20°C for about 30 min; the amine **AA4** (380 mg, 0.49 mm) and DIEA (63 mg, 0.49 mm) in DCM (3 mL) were then added, stirred at about -20°C for about 30 min and then at about rt

for about 16 h. Solid urea **AA5** precipitated out, was filtered and air dried. Pyrrolidine (90 mg, 1.25 mm) was added to glacial acetic acid (5.0 mL) under argon and formaldehyde (37%, 0.10 g, 1.25 mm) was added; the reaction was stirred at about rt for about 25 min. The indole urea **AA5** (0.43 g, 0.42 mm)
5 was added and the reaction stirred at about rt for about 2 h. The solution was evaporated *in vacuo* to an oil, which was partitioned between chloroform in 2-propanol (10:1, 75 mL) and 1N NaOH (30 mL). The organic layer was washed with saturated NaHCO₃ (2X), brine (2X) and dried (K₂CO₃), then evaporated *in vacuo* to a tan solid. This solid was stirred with TFA:DCM:anisole (50:50:1; 40
10 mL) at about rt for about 3 h and evaporated *in vacuo* to an oil. The resulting oil was triturated with ethyl ether (3X) to give the product Compound **15** as an off-white solid. H-1 NMR 1.4 - 2.0 (m, 8 aliphatics), 3.0 - 3.3 (m, 6H), 4.1 (dd, 2H), 4.2 - 4.4 (m, 5H), 4.6 (dd, 2H), 5.4 (s, 2H, CH₂), 7.05 (s, 1H, indole H₂), 7.1 - 7.7 (m, 14H, aromatics), 7.9 (s, 1H, indole H₇); MS *m/z* 828 (MH⁺).

15

SCHEME AA



Example 2

5

Synthesis of Compound 6 (See Scheme AB)

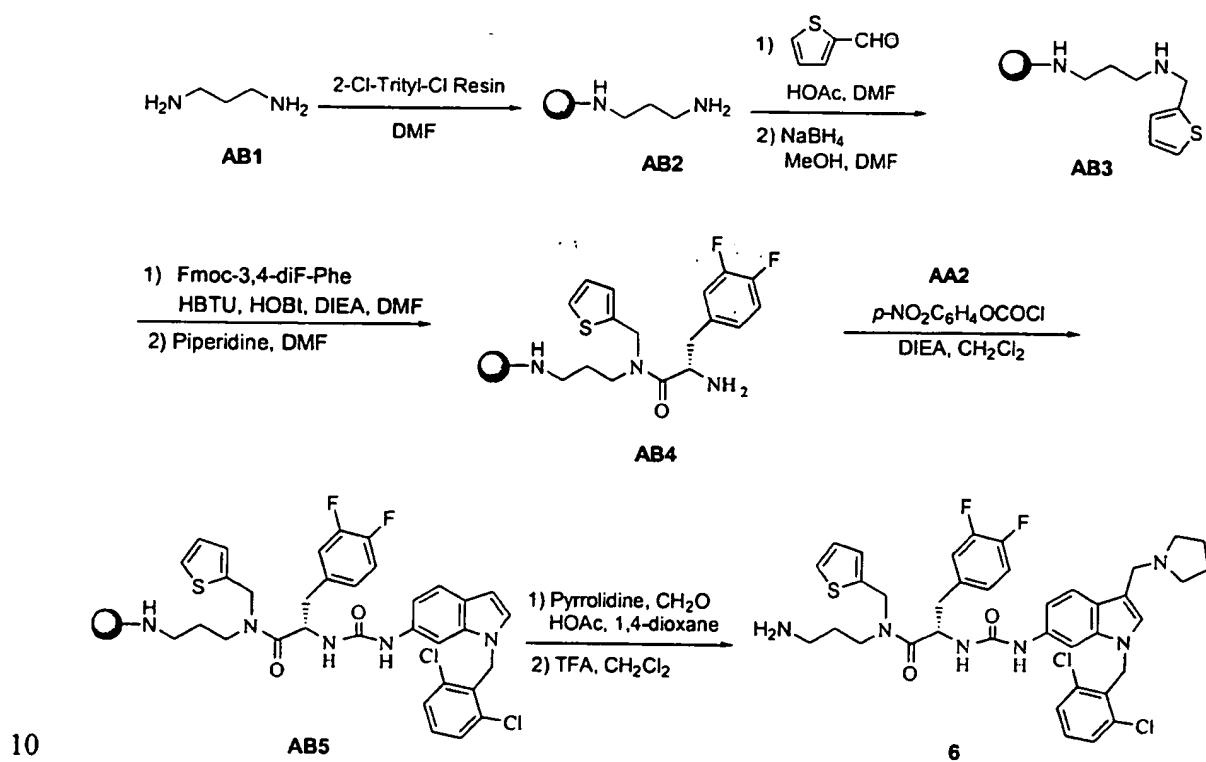
Benzene propanamide, *N*-(3-aminopropyl)-*N*-(2-thiophenemethyl)-[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1*H*-indol-6-yl]amino]carbonyl]amino]-3,4-difluoro-, (S)- (Compound 6)

10

As shown in Scheme AB, following, 2-Chlorotriyl chloride resin (4.5 g, 8.1 mmol) was stirred in dried DMF (80 mL) as 1,3-diaminopropane (**AB1**) (18.0 g, 243 mmol) was added. The reaction was stirred at about rt for about 20 h. The resin **AB2** was filtered on a sintered glass funnel and washed with DMF 5 (4X), MeOH (3X), and DCM (3X) and dried *in vacuo* to give the resin **AB2**. A portion of the resin **AB2** (300 mg) was placed in a solid-phase hour-glass reactor and agitated (nitrogen bubbling) in DMF (8 mL) with 2-thiophenecarboxaldehyde (467 mg, 4.2 mmol) and HOAc (100 mL) for about 1.5 h. The solution was drawn off and the resin was washed with dried DMF 10 (3X), suspended in dried DMF (8 mL) and then re-treated with 2-thiophenecarboxaldehyde (467 mg, 4.2 mmol) and HOAc (100 mL) for about another 0.5 h. The resulting solution was drawn off and the resin was washed with dried DMF (3X). To the resin was added dried DMF (8 mL) and MeOH (3 mL), then immediately followed by NaBH₄ (200 mg, 5.3 mmol). The mixture 15 was agitated (nitrogen bubbling) at about rt for about 1.5 h and then filtered, washed with MeOH, DMF and DCM and dried *in vacuo* to afford the resin **AB3**. A portion of the resin **AB3** (160 mg) was suspended in DMF (4 mL) and treated with Fmoc-3,4-diF-Phe-OH (220 mg, 0.52 mmol), HOBT (85 mg, 0.63 mmol), DIEA (162 mg, 1.25 mmol) and HBTU (237 mg, 0.63 mmol). The suspension 20 was stirred at about rt for about 20 h, then filtered and washed with DMF, MeOH and DCM. The resulting resin was treated with 20% piperidine in DMF (4 mL) at about rt for about 2 h and then filtered, washed with DMF, MeOH, DCM and Et₂O to afford the resin **AB4**. To 4-Nitrophenyl chloroformate (157 mg, 0.78 mmol) in dry DCM (15 mL) at about -20°C, a solution of **AA2** 25 (Scheme AA, 291 mg, 1.0 mmol) and DIEA (291 mg, 2.25 mmol) in DCM (5 mL) was added dropwise. The mixture was stirred at about -20°C for about 20 min and then the dipeptidyl resin **AB4** was added. After additional stirring at about -20°C for about 20 min, the reaction temperature was allowed to warm up to about rt slowly, then stirred at about rt for about 18 h. The suspension 30 was filtered and washed with DMF, MeOH, DCM and Et₂O, then dried *in vacuo* to give the resin **AB5**. Half of the resin **AB5** was treated with a solution of pyrrolidine (85 mg, 1.2 mmol) and formaldehyde (37%, 78 mg, 0.96 mmol) in 1,4-dioxane:glacial acetic acid (4:1; 4 mL). The suspension was stirred at

about rt for about 18 h, then filtered, washed with MeOH, DCM and Et₂O and dried *in vacuo*. The resulting resin was treated with TFA:DCM:anisole (50:50:0.50, 5 mL) at about rt for about 1.5 h; then the reaction mixture was filtered and washed with fresh 30% TFA in DCM. The filtrates were combined and evaporated *in vacuo*, and the residue was triturated with diethyl ether (2X) to give the product Compound 6 as a light yellow solid. ¹H NMR (CD₃OD) 7.81 - 6.95 (m, 13 H), 5.56 (s, 2 H), 5.05 - 4.80 (m, 3 H), 4.45 (s, 2 H), 3.45 - 2.82 (m, 10 H), 2.20 - 1.80 (m, 6 H). ES-MS *m/z* 753 (MH⁺).

Scheme AB



Example 3

15

As a specific embodiment of an oral composition, about 100 mg of the Compound 15 of Example 1 is formulated with sufficient finely divided lactose to

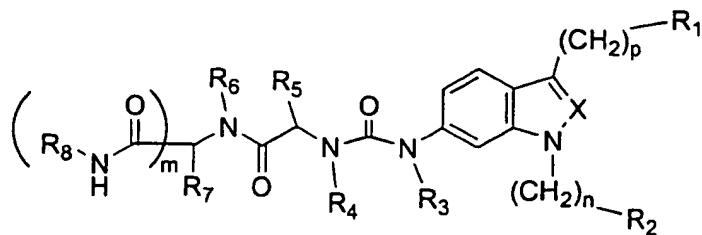
provide a total amount of about 580 mg to about 590 mg to fill a size O hard gel capsule.

5 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of the following formula (I):

5



(I)

wherein:

10

R₁ is selected from the group consisting of amino, C₁-C₈ alkylamino, C₁-C₈ dialkylamino, arylamino, arC₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, heteroalkylC₁-C₈ alkylamino, heteroalkyl C₁-C₈ alkyl-N-methylamino, C₁-C₈ dialkylamino C₁-C₈ alkylamino, -N(C₁-C₈ alkyl)-C₁-C₈ alkyl-N(C₁-C₈ alkyl)₂, -N(C₁-C₈ alkyl)(C₁-C₈ alkenyl), -N(C₁-C₈ alkyl)(C₃-C₈ cycloalkyl), heteroalkyl and substituted heteroalkyl, wherein the substituent on the heteroalkyl is selected from oxo, amino, C₁-C₈ alkoxy, C₁-C₈ alkyl, C₁-C₈ alkylamino or C₁-C₈ dialkylamino;

15

R₂ is selected from the group consisting of unsubstituted or substituted aryl, arC₁-C₈ alkyl, C₃-C₈ cycloalkyl and heteroaryl, wherein the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from the group consisting of one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

20

R₃ is selected from the group consisting of H and C₁-C₈ alkyl;

25

R₄ and R₅ are each independently selected from the group consisting of

30

H, C₁-C₈ alkyl, aminoC₁-C₈ alkyl, amidinoC₁-C₈ alkyl, guanidinoC₁-C₈ alkyl, aryl, arC₁-C₈ alkyl, substituted aryl, substituted arC₁-C₈ alkyl, heteroaryl,

heteroarylC₁-C₈ alkyl, substituted heteroaryl, substituted heteroarylC₁-C₈ alkyl, C₃-C₆ cycloalkyl and substituted C₃-C₆cycloalkyl, wherein the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from the group consisting of one or more of halogen, nitro, amino, amidino, 5 guanidino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

R₆ and R₇ are each independently selected from the group consisting of H, C₁-C₈ alkyl, aminoC₁-C₈ alkyl, aminoC₃-C₈ cycloalkyl, amidinoC₁-C₈ alkyl, 10 guanidinoC₁-C₈ alkyl, aryl, substituted aryl, arC₁-C₈ alkyl, substituted arC₁-C₈ alkyl, heteroarylC₁-C₈ alkyl and substituted heteroarylC₁-C₈ alkyl, wherein the one or more substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from the group consisting of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ 15 alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

R₈ is selected from the group consisting of H, C₁-C₈ alkyl, amino C₁-C₈ alkyl, allyl, C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl, aryl, substituted aryl, 20 C₁-C₈ alkyl, substituted arC₁-C₈ alkyl, heteroaryl, substituted heteroaryl, heteroarylC₁-C₈ alkyl and substituted heteroarylC₁-C₈ alkyl, wherein the one or more substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from the group consisting of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ 25 alkoxycarbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

X is CH or N;

30 n is an integer selected from the group consisting of 0, 1, 2 and 3;
m is an integer selected from the group consisting of 0 and 1; and
p is an integer selected from the group consisting of 1 and 2;

provided that when m is 1, then one of R_5 or R_7 must be hydrogen;

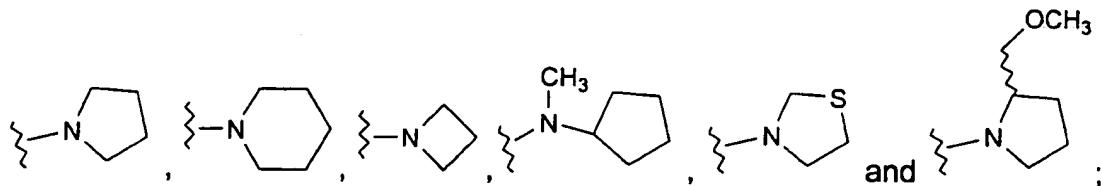
provided further that when R_5 is hydrogen, then R_4 cannot be hydrogen; and, when R_7 is hydrogen, then R_6 cannot be hydrogen;

5

and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein

10 R_1 is selected from the group consisting of dimethylamino, diethylamino, di-(*n*-propyl)amino,



15 R_2 is selected from the group consisting of unsubstituted or substituted aryl, arC₁-C₆ alkyl, C₃-C₆ cycloalkyl and heteroaryl, where the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one to three substituents selected from the group consisting of halogen, cyano, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

20

R_3 is selected from the group consisting of H and C₁-C₄ alkyl;

25 R_4 and R_5 are each independently selected from the group consisting of H, C₁-C₄ alkyl, aminoC₁-C₆ alkyl, amidinoC₁-C₆ alkyl, guanidinoC₁-C₆ alkyl, aryl, arC₁-C₈ alkyl, substituted aryl, and substituted arC₁-C₈ alkyl, wherein from one to two substituents on the aryl or aralkyl are independently selected from the group consisting of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

30

R₆ and R₇ are each independently selected from the group consisting of H, C₁-C₄ alkyl, aminoC₁-C₆ alkyl, amidinoC₁-C₆ alkyl, guanidinoC₁-C₆ alkyl, aryl, substituted aryl, arC₁-C₆ alkyl, substituted arC₁-C₆ alkyl, C₃-C₆ cycloalkylC₁-C₆ alkyl, heteroarylC₁-C₆ alkyl and substituted heteroarylC₁-C₆ alkyl, wherein the 5 one to two substituents on the aryl, aralkyl, or heteroaryl group are independently selected from the group consisting of halogen, nitro, amino, amidino, guanidino, cyano, hydroxyalkyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

10

R₈ is selected from the group consisting of H, C₁-C₆ alkyl, aminoC₁-C₆ alkyl, aryl, substituted aryl, arC₁-C₆ alkyl, and substituted arC₁-C₆ alkyl, wherein one or more of the substituents on the aryl or aralkyl group are independently selected from the group consisting of halogen, nitro, amino, amidino, 15 guanidino, cyano, hydroxyalkyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, acetyl, fluorinated C₁-C₄ alkyl, fluorinated C₁-C₄ alkoxy and C₁-C₄ alkylsulfonyl;

n and p are both 1;

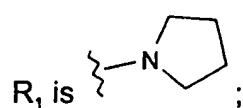
20

provided that when m is one, then one of R₅ or R₇ must be hydrogen;

and provided further that when R₅ is hydrogen, then R₄ cannot be hydrogen; and, when R₇ is hydrogen, then R₆ cannot be hydrogen;

25 and pharmaceutically acceptable salts thereof.

3. The compound of Claim 2, wherein



30

R₂ is unsubstituted or substituted phenyl wherein the substituent is one or two substituents selected from the group consisting of fluorine, chlorine, iodine, methyl, cyano and trifluoromethyl;

5 R₃ is H;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of H, aminoC₁-C₅ alkyl, amidinoC₁-C₅ alkyl, guanidinoC₁-C₅ alkyl, C₃-C₈ cycloalkylC₁-C₆ alkyl, heteroarylC₁-C₆ alkyl, benzyl and substituted benzyl
10 wherein the substituents on the benzyl are one to two substituents independently selected from the group consisting of chlorine, fluorine, methyl and trifluoromethyl;

15 R₈ is benzyl;

provided that when m is one, then one of R₅ or R₇ must be hydrogen;

and provided further that when R₅ is hydrogen, then R₄ cannot be
20 hydrogen; and, when R₇ is hydrogen, then R₆ cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3, wherein

25

R₂ is 2,6-dichlorophenyl or 2-methylphenyl;

provided that when m is one, then one of R₅ or R₇ must be hydrogen;

30 and provided further that when R₅ is hydrogen, then R₄ cannot be hydrogen; and, when R₇ is hydrogen, then R₆ cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.
- 5 6. A pharmaceutical composition made by mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.
7. A process for making a pharmaceutical composition comprising mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.
- 10 8. A method of treating a condition selected from the group consisting of thrombosis, restenosis, hypertension, heart failure, arrhythmia, myocardial infarction, glomerulonephritis, reocclusion following thrombolytic therapy, reocclusion following angioplasty, inflammation, angina, stroke, atherosclerosis, ischemic conditions, a vaso-occlusive disorder, neurodegenerative disorders, Angiogenesis related disorders and cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.
- 15 9. The method of Claim 8, wherein the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.
- 20 10. A method of treating a condition selected from the group consisting of thrombosis, restenosis, hypertension, heart failure, arrhythmia, myocardial infarction, glomerulonephritis, reocclusion following thrombolytic therapy, reocclusion following angioplasty, inflammation, angina, stroke, atherosclerosis, ischemic conditions, a vaso-occlusive disorder, neurodegenerative disorders, Angiogenesis related disorders and cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 5.
- 25 30 11. The method of Claim 10, wherein the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.

12. A method of inhibiting platelet aggregation in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.

5

13. The method of Claim 12, wherein the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.

14. A method of inhibiting platelet aggregation in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 5.

15. The method of Claim 14, wherein the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.

15

16. A method of treating a condition mediated by thrombin receptor (PAR-1) in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.

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17. The method of Claim 16, wherein the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.

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18. A method of treating a condition mediated by thrombin receptor (PAR-1) in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 5.

19. The method of Claim 18, wherein the therapeutically effective amount of the compound is from about 0.1 mg/kg/day to about 300 mg/kg/day.

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/18021

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/14 C07D231/56 A61K31/4045 A61K31/416 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 00357 A (VERTEX PHARMA) 7 January 1999 (1999-01-07) page 2, line 13 - line 22 page 5, line 1 -page 6, line 10 page 25, compounds no.81, 82, 85; page 26, compound no. 86 claims 1,9-12 ---	1,5,8, 10,16,18
A,P	WO 99 33798 A (OGAMI TETSURO ;KAWAMINAMI EIJI (JP); MATSUMOTO YUZO (JP); OKADA MI) 8 July 1999 (1999-07-08) abstract page 28 -page 32 ---	1,5,8,10
A	US 4 977 153 A (LOUIS WILLIAM J ET AL) 11 December 1990 (1990-12-11) column 7 -column 12; claims 1,13,14 ---	1,5,8,10 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

2 November 2000

10/11/2000

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INTERNATIONAL SEARCH REPORT

Internat	Application No
PCT/US 00/18021	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 439 906 A (BOCK MARK G ET AL) 8 August 1995 (1995-08-08) abstract; claims 1,5; examples 10,15 ---	1,5,8,10
A	WO 93 18026 A (BEECHAM GROUP PLC) 16 September 1993 (1993-09-16) claims 1,36-40; examples 1-27; table 1 ---	1,5
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 00/18021

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